PREPARATION AND BIOLOGICAL ACTIVITY OF A NUMBER OF COMPOUNDS OF THE ACETYLENE SERIES

O. A. Malchenko, N. P. Soboleva, N. V. Zotchik, L. G. Pavlovskaya, and I. A. Rubtsov

UDC 282:547.314.2/.012.1

The discovery among naturally occurring materials of a considerable number of acetylene derivatives has been reported during the last few years. About 180 such compounds have been isolated from the higher plants as well as from microorganisms [1]. The compounds are of the most diverse structures and among them occur a number of antibiotics and fungicides. The antibiotics include mycomycin (3,5,7,8-tridecatetraen-10,11-diynoic acid, $CH\equiv C-C\equiv C-CH=C=CH-CH=CH-CH=CH-CH_2-CO_2H$), agrocybin (8-hydroxy-2,4,6-octatriynamide, $HO\cdot CH_2-C\equiv C-C\equiv C-C\equiv C-CONH_2$), and diatretyne nitrile (nudic acid B, $NC-C\equiv C-C\equiv C-CH=CH-CO_2H$), while of special interest in this connection is capillin (I):

$$C_6H_5-CO-C\equiv C-C\equiv C-CH_3$$
I

(obtained from Artemisia capillaris, Thunb. [2]) which has proved to be one of the most powerful of the currently known fungicides. Various ana- and homologs of capillin

$$R-CO-C\equiv C-C\equiv C-R' \quad R = Alk, Ar$$
$$R-CO-C\equiv C-CH=CH-R' \quad R = Alk, Ar$$

also show biological activity.

The instability of these polyunsaturated compounds gives rise to considerable difficulties in handling them and so narrows the choice of methods which might otherwise be available for their preparation. Seeing, however, that the trialkylsilyl group is known [3] to increase the stability of acetylenic compounds, we have examined, and indeed perfected, a new method of using various such silicon derivatives for the preparation of polyunsaturated compounds related to (I) and its analogs, and having the general structure:

$$R-CO-C\equiv C-\underset{\displaystyle R'}{\underset{|}{C}}=CH-R''$$
$$R = C_6H_5,\ CH_3;\ R' = CH_3;\ R'' = H$$

Our process is shown in the following flowsheet diagram:

$$(C_2H_5)_3SiC\equiv CH \xrightarrow[2.\,CH_3COCH_3]{1.\,C_2H_5MgBr} (C_2H_5)_3SiC\equiv C-\underset{\displaystyle OH}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}-CH_3 \rightarrow (C_2H_5)_3SiC\equiv C-\overset{\displaystyle CH_3}{\overset{|}{C}}$$
II III IV

$$=CH_2 \xrightarrow{RCOCl} R-\underset{\displaystyle V}{CO}-C\equiv C-\overset{\displaystyle CH_3}{\overset{|}{C}}=CH_2$$
a) $R = CH_3$
b) $R = C_6H_5$

The method, as compared with that hitherto available [4], not only improves the yield at stages (III) (formation of the ynol) and (IV) (dehydration), but permits also of the preparation of the ketone (V) from the hydration product (IV) in a single operation; the overall yield of end-product itself is increased from 26 to 50%.

Moscow Technological Institute of the Food Industry. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 8, No. 8, pp. 6-9, August, 1974. Original article submitted June 22, 1973.

3-Methyl-1-(triethylsilyl)but-1-yn-3-ol (III) was obtained reacting triethylsilylacetylene (II) with ethyl magnesium bromide in ethereal solution followed by condensation with acetone in the same solvent. Dehydration of (III) to (IV) was carried out by warming in benzene solution with a catalytic amount of 4-toluenesulfonic acid, while the subsequent replacement of the triethylsilyl residue by the benzoyl radical, to furnish (V), was effected by means of benzoyl chloride.

The available literature data [2] indicate that (I) and its analogs exercise an irritant effect and can therefore be used as fungicides only in vitro. Moreover, certain analogs of (I) are so unstable as not to be applicable in practice at all. For these reasons it appeared to us of interest to prepare and examine the biological action of trialkylsilylacetylene derivatives structurally analogous with (I). Compounds of this type have not hitherto been subjected to biological investigation, although it is known that many organic compounds of silicon do show biological activity.

The compound (VII), an analog of capillin (I) in which the methyl group has been replaced by the triethylsilyl residue, was prepared from

$$2(C_2H_5)_3SiC\equiv CH \rightarrow \underset{II}{(C_2H_5)_3SiC\equiv C-C\equiv C-Si(C_2H_5)_3} \xrightarrow{RCOCl} \underset{VI}{R-CO-C\equiv C-C\equiv C-Si(C_2H_5)_3}$$

$$\rightarrow \underset{VII}{R-CO-C\equiv C-C\equiv C-Si(C_2H_5)_3}$$

(a) R = CH_3, (b) R = C_6H_5

1,4-bis(triethylsilyl)-1,3-butadiyne (VI) which, in its turn, was obtained by the oxidative union of two molecules of (II) in methanol solution in the presence of a catalytic proportion of cuprous chloride [4]. We established that a triethylsilyl group in (VI) could be replaced by acyl or benzoyl radicals just as an analogous reaction can be carried through with disilylacetylene. The resulting silyldiacetylenic ketones (VII) could not be purified by distillation in vacuo or by chromatography on alumina. The only satisfactory method proved to be preparative chromatography on silica gel.

The silyldiacetylenic ketones (VII) prepared by this method were markedly more stable than the silicon-free capillin analogs (Va) and (Vb). The compounds showed biological activity, and since this could be connected either with the diyne feature of the molecule, or else with the carbonyl group situated in the α-position to an acetylenic linkage, the preparation of compounds (IX) and (XI) was next undertaken in order to settle the issue. The compound (IX), 5-phenyl-1-(triethylsilyl)-5-heptaen-1,3-diyne, contains, by contrast with the ketones (VII), no carbonyl group, while the compound (XI), 3-phenyl-1-(trimethylsilyl)-1-propyn-3-one, is distinguished from (VII) by the presence of only one acetylenic linkage. Compound (IX) was obtained

$$\underset{VII\,б}{C_6H_5-CO-C\equiv C-C\equiv C-Si(C_2H_5)_3} \qquad \underset{X}{(CH_3)_3SiC\equiv C-Si(CH_3)_3}$$

$$\downarrow C_2H_5MgBr \qquad\qquad \downarrow C_6H_5COCl$$

$$\underset{VIII}{CH_3-CH_2-\overset{\displaystyle C_6H_5}{\overset{|}{\underset{\displaystyle OH}{\underset{|}{C}}}}-C\equiv C-C\equiv C-Si(C_2H_5)_3} \qquad \underset{XI}{C_6H_5-CO-C\equiv C-Si(CH_3)_3}$$

$$\rightarrow CH_3-CH=\overset{\displaystyle C_6H_5}{\overset{|}{C}}-\underset{IX}{C\equiv C-C\equiv C-Si(C_2H_5)_3}$$

by condensing (VIIb) with a Grignard reagent (EtMgBr) followed by dehydration; compound (XI) was prepared by the interaction of bis-(trimethylsilyl)acetylene (X) with benzoyl chloride.

Of the several compounds examined for biological activity, only (IX) gave a negative result. Evidently, therefore, biological activity in compounds of the type here in question is determined by the presence of an α-ketoacetylenic group, $-\overset{\displaystyle O}{\overset{\|}{C}}-C\equiv C-$.

The compounds (Vb), (VII), and (XI) show a high fungicidal activity against pathogenic mycetes, and can kill Trichophyton gypseum and T. rubrum in 5 min; compound (IX) was ineffective even after exposing the organisms to its influence for 2 h.

The biological tests were carried out in accordance with the test-object method approved by the All-Union Scientific-Research Institute for Disinfection and Sterilization.

EXPERIMENTAL

3-Methyl-1-(triethylsilyl)but-1-yn-3-ol (III). A solution of (II) (26 g) in absolute ether (30 ml) was added to one of ethyl magnesium bromide (obtained from 4.3 g metallic magnesium, 18 ml of ethyl bromide, and 100 ml of absolute ether). The mixture was boiled for 3 h, the resulting reaction mass then treated at 0°C with a solution of acetone (23 ml) in absolute ether (20 ml), and finally stirred at room temperature for 2 h. To isolate the product, diluted hydrochloric acid (1 : 3) was added at 0°, the resulting layers separated, and the aqueous layer reextracted with three 30-ml portions of ether. The total ethereal solution so obtained was washed with two 15-ml portions of a 5% aqueous solution of sodium bicarbonate and dried over anhydrous magnesium sulfate. It furnished 30.5 g (87%) of (III), bp 90-92° (3 mm), $n_D^{20°}$ 1.4540; IR spectrum, 2180 cm^{-1} (C≡C), 3450 cm^{-1} (OH). Found %: C 66.35; H 10.9 $C_{11}H_{22}SiO$. Calculated, %: C66.6; H 11.1.

3-Methyl-1-(triethylsilyl)-3-buten-1-yne (IV). The preceding compound (III) (30 g) was treated with 4-toluenesulfonic acid (0.4 g) and warmed in boiling benzene. The toluenesulfonic acid was then eliminated by filtration through alumina. The yield of (IV) was 22.4 g (63%), bp 80-82° (3 mm), $n_D^{20°}$ 1.4640.

2-Methyl-5-phenyl-1-penten-3-yn-5-one (Vb).* The mixture assumed a dark brown color. After stirring at the same temperature for 30 min, 25 ml of diluted hydrochloric acid (1 : 3) was added at 0 to −5°. The resulting layers were separated and worked up in the customary manner, the ethereal solution so obtained being dried over calcium chloride. This gave 6.05 g (69%) of (Vb), bp 115-117° (1 mm), $n_D^{20°}$ 1.5650. The 2,4-dinitrophenylhydrazone was an orange-colored microcrystalline powder, mp 174-175°(from ethanol). The literature [5] gives for this compound, (Vb), bp 110° (0.3 mm), $n_D^{20°}$ 1.5657, 2,4-dinitrophenylhydrazone, mp 175°.

2-Methyl-1-hexen-3-yn-5-one (Va). Yield, 88.7%; bp 46-50° (6 mm); $n_D^{20°}$ 1.4463. The 2,4-dinitrophenylhydrazone, orange-colored microcrystalline powder, had mp 123-124°. Found %: N 18.74; $C_{14}H_{14}N_4O_4$; Calculated %: N 18.74.

1,4-Bis(triethylsilyl)-1,3-butadiyne (VI). A stream of air was passed for 5 h through a mixture of (II) (22 g), cuprous chloride (0.42 g), pyridine (2.4 ml), and methanol (45 ml) kept at 30-35°. The reaction mixture was then stirred for a further 8 h and finally decomposed by the addition of an aqueous solution of ammonium chloride. The resulting layers were separated, and the aqueous layer extracted with ether. The extract, dried over anhydrous magnesium sulfate, furnished 13.3 g (71%) of (VI), bp 144-145° (1 mm), $n_D^{20°}$ 1.5040. The literature [4] gives bp 139-140° (0.4 mm), $n_D^{20°}$ 1.5040.

5-Phenyl-1-(triethylsilyl)-1,3-pentadiyn-5-one (VIIb). A mixture of (VI) (10 g), benzoyl chloride (4.5 ml), and methylene dichloride (12 ml) was added at 0° to one of aluminum trichloride (5.2 g) and methylene dichloride (25 ml). The reaction mixture, which assumed a dark brown color, was stirred at the same temperature for a further 30 min and then decomposed by the addition of diluted acid at 0 to −5°. After working up in the usual way, the final ether extracts were dried over calcium chloride. The solvent was removed in a vacuum to give a residue (14.3 g) of crude (VIIb). This product was purified by preparative chromatography using silica gel containing 13% calcium sulfate; the adsorbent was of mesh grade 0.125 μ, and the solvent system employed was hexane–benzene (1 : 1), R_f 0.83. By this means 4 g of the crude material furnished 1.62 g (60.5%) of (VIIb), $n_D^{20°}$ 1.5380, IR spectrum, 2180 cm^{-1} (−C≡C−) and 1735 cm^{-1} (C=O). Found %: C 76.86; H 7.5. $C_{17}H_{20}OSi$. Calculated %: C 76.1; H 7.46. The 2,4-dinitrophenylhydrazone had mp 193-195°.

1-(Triethylsilyl)-1,3-hexadiyn-5-one (VIIa). This compound was obtained in 73% yield, $n_D^{20°}$ 1.4750, R_f 0.75. Found %: C 67.35; H 8.7. $C_{12}H_{18}OSi$. Calculated %: C 69.9; H 8.74. The 2,4-dinitrophenylhydrazone had mp 133-135°.

5-Phenyl-1-(triethylsilyl)-1,3-heptadiyn-5-ol (VIII). Unpurified (VIIb) (14.3 g) was treated at 20° with a solution of ethyl magnesium bromide (obtained from 1.9 g metallic magnesium, 12.3 ml ethyl bromide, and 100 ml of absolute ether). The mixture was stirred at this temperature for 1 h, then cooled to 0° and treated with diluted hydrochloric acid (1 : 3). The resulting layers were separated and, after the customary work-up procedure, the ethereal layer was dried over anhydrous magnesium sulfate. This gave 6.27 g of (VIII); the yield was 58.4% calculated on the compound (VI); bp 175-178° (1 mm), $n_D^{20°}$ 1.5500. IR spectrum, 2105 cm^{-1} (−C≡C−) and 3400 cm^{-1} (OH). Found %: C 77.1; H 8.6. $C_{19}H_{26}OSi$. Calculated %: C 76.5; H 8.7.

5-Phenyl-1-(triethylsilyl)-5-hepten-1,3-diyne (IX). The preceding compound (VIII) (6.27 g) was treated with 4-toluenesulfonic acid (0.1 g) and warmed in boiling benzene. The toluenesulfonic acid was then

*Portion of text missing in Russian original – Publisher.

eliminated by filtration through alumina. The crude product so obtained was purified by chromatography through aluminum oxide of grade II activity followed by elution with hexane. This gave (IX) (5.5 g, 83.5%), n_D^{20} 1.5710, IR spectrum, 2180 cm^{-1} (−C≡C−). Found %: C 81.9; H 8.4. $C_{19}H_{24}Si$. Calculated %: C 81.6; H 8.56.

LITERATURE CITED

1. F. Bohlmann, Chimia, 16, 353 (1962).
2. K. Imai, J. Pharm. Soc. Japan, 76, 405 (1956).
3. A. D. Petrov and S. I. Sadykhzade, Dokl. Akad. Nauk SSSR, 85, No. 6, 1297 (1952).
4. R. Eastmond, T. R. Johnson, and D. R. M. Walton, Tetrahedron, 28, 4601 (1972).
5. B. W. Nash, D. A. Thomas, W. K. Warburton, and Thelma D. Williams, J. Chem. Soc., 2983 (1965).